

Research Article

Investigation of the Chemical Changes from Crude and Processed Paeoniae Radix Alba-Atractylodis Macrocephalae Rhizoma Herbal Pair Extracts by Using Q Exactive High-Performance Benchtop Quadrupole-Orbitrap LC-MS/MS

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The Paeoniae Radix Alba-Atractylodis Macrocephalae Rhizoma herbal pair is mainly used for regulating the functions of liver and spleen, benefiting *qi*, and nourishing blood. However, the bioactive compounds for the pharmacological activities of the crude and processed Paeoniae Radix Alba-Atractylodis Macrocephalae Rhizoma herbal pair extracts are still unclear to date. In the present study, Q Exactive high-performance benchtop quadrupole-Orbitrap LC-MS/MS was applied to identify the complicated components from crude and processed Paeoniae Radix Alba, crude and processed Atractylodis Macrocephalae Rhizoma, and their crude and processed herbal pair extracts. 123 and 101 compounds were identified in crude and processed Paeoniae Radix Alba samples, respectively. Meanwhile, 32 and 26 compounds were identified in crude and processed Atractylodis Macrocephalae Rhizoma samples, respectively. In the crude and processed Paeoniae Radix Alba-Atractylodis Macrocephalae Rhizoma herbal pair extracts, co-decoction could significantly change the chemical composition of Paeoniae Radix Alba and Atractylodis Macrocephalae Rhizoma in solution. The developed method may provide a scientific foundation for deeply elucidating the processing and compatibility mechanism of Paeoniae Radix Alba and Atractylodis Macrocephalae Rhizoma.

1. Introduction

Traditional Chinese medicine (TCM) processing is regarded as a pharmaceutical technology based on TCM theory, the requirements of different syndrome treatment, the quality nature of medicine, and different demands of clinical dispensing and preparations [1]. It is one of the characteristics in application of TCM. The compatible components of prescription are composed of prepared Chinese crude drugs after TCM processing.

The prescription compatibility and TCM processing are not only two major features of clinical medication in TCM, but are also critical to distinguish TCM from natural medicine. The research on structural features, compatible

effect, and material basis of the herbal pair is the important support in the study of the prescription compatibility since the herbal pair is the minimum unit in prescription of TCM [2, 3]. They play a guidance and significant role in reveal of the compatibility rule and the scientific connotation. The herbal pair compatibility theory can explain the relationship of the prescription compatibility to some extent. The research on the relationship between the herbal pair compatibility and the prescription compatibility contributes to the elucidation of the prescription compatibility mechanism and the action mechanism of treatment. There are many herbal pairs commonly used in the clinical practice of TCM, such as the herbal pairs of *Paeonia Lactiflora*-*Liquorice*, *Ginseng*-*Aconite*, and *Aconite*-*Rhizome Zingiberis* [4, 5] besides the

TABLE 1: Major chemical constituents identified in crude and processed *Paeoniae Radix Alba* and in crude and processed *Paeoniae Radix Alba-Atractylodis Macrocephalae Rhizoma* herbal pair.

No.	t_R (min)	Compound name	Formula	Paeoniae Radix Alba		Paeoniae Radix Alba-Atractylodis Macrocephalae Rhizoma herbal pair	
				(Measured area)		(Measured area)	
				Crude	Processed	Crude	Processed
1	0.84	6-O-galloylsucrose	C ₁₉ H ₂₆ O ₁₅	1.8570E + 08	1.9012E + 08	4.2870E + 07	4.4158E + 07
2	0.84	Glucogallin	C ₁₃ H ₁₆ O ₁₀	2.9739E + 08	2.5698E + 08	1.0931E + 08	—
3	1.05	Desbenzoylpaeoniflorin	C ₁₆ H ₂₄ O ₁₀	1.6682E + 08	1.6263E + 08	9.8500E + 07	—
4	1.06	1'-O-galloylsucrose	C ₁₉ H ₂₆ O ₁₅	3.2574E + 08	2.9123E + 08	—	—
5	1.07	1-O-glucopyranosyl paeonisuffrone	C ₁₆ H ₂₄ O ₉	2.8667E + 08	2.3654E + 08	1.1532E + 08	—
6	1.13	Gallic acid	C ₇ H ₆ O ₅	4.1152E + 09	4.0736E + 09	2.7186E + 09	3.1711E + 09
7	1.18	Oxypaeoniflorin sulfonate	C ₂₃ H ₂₈ O ₁₄ S	4.9527E + 07	3.5407E + 07	6.1568E + 06	8.5010E + 07
8	1.22	Ethyl gallate	C ₉ H ₁₀ O ₅	5.1351E + 07	6.7200E + 07	1.5592E + 07	4.8337E + 07
9	1.22	6-O-galloyl desbenzoylpaeoniflorin	C ₂₃ H ₂₈ O ₁₄	9.9020E + 07	9.5040E + 07	5.3798E + 07	—
10	1.26	6-O-glucopyranosyl- lactinolide	C ₁₆ H ₂₆ O ₉	1.0875E + 08	1.1180E + 08	—	3.7130E + 07
11	1.30	Paeoniflorin sulfonate I	C ₂₃ H ₂₈ O ₁₃ S	5.3777E + 07	3.6391E + 07	7.3077E + 06	7.7185E + 07
12	1.30	Mudanpioside E sulfonate	C ₂₄ H ₃₀ O ₁₅ S	5.3777E + 07	3.6391E + 07	7.3077E + 06	7.7185E + 07
13	1.43	6-O-glucopyranosyl- lactinolide	C ₁₆ H ₂₆ O ₉	7.4342E + 08	6.5904E + 08	4.0712E + 08	3.1407E + 08
14	1.64	Mudanpioside F	C ₁₆ H ₂₄ O ₈	6.4178E + 08	6.0980E + 08	4.0130E + 08	6.6680E + 07
15	1.76	Isomaltopaeoniflorin sulfonate	C ₂₉ H ₃₈ O ₁₈ S	1.8858E + 09	1.1382E + 09	2.6277E + 08	5.8622E + 07
16	1.81	Pedunculagin	C ₃₄ H ₂₄ O ₂₂	4.8098E + 07	—	5.6076E + 07	1.2660E + 09
17	1.97	Paeoniflorin sulfonate I	C ₂₃ H ₂₈ O ₁₃ S	3.1881E + 10	2.3387E + 10	6.6202E + 09	5.5241E + 10
18	2.25	Oxypaeoniflorin	C ₂₃ H ₂₈ O ₁₂	2.3173E + 09	2.4115E + 09	1.6734E + 09	1.4513E + 09
19	2.36	Gallotannin	C ₂₇ H ₂₄ O ₁₈	2.2850E + 08	2.2458E + 08	1.6284E + 08	1.6703E + 08
20	2.37	1-O-benzoylsucrose	C ₁₉ H ₂₆ O ₁₂	1.3761E + 08	1.3161E + 08	1.1673E + 08	8.2986E + 07
21	2.41	d-catechin	C ₁₅ H ₁₄ O ₆	3.7822E + 09	4.2278E + 09	2.6339E + 09	2.5982E + 09
22	2.63	Methyl gallate	C ₈ H ₈ O ₅	2.3823E + 10	2.4116E + 10	2.3388E + 10	—
23	2.63	Salicylic acid	C ₇ H ₆ O ₃	2.3823E + 10	2.4116E + 10	2.3388E + 10	1.7399E + 10
24	2.72	Albiflorin R1	C ₂₃ H ₂₈ O ₁₁	5.2469E + 08	5.6725E + 08	5.6329E + 08	4.5647E + 08
25	3.00	Kaempferol-3,7-di-O- glucoside	C ₂₇ H ₃₀ O ₁₆	3.8065E + 07	2.1896E + 07	3.5719E + 07	1.5513E + 07
26	3.00	Paeonoside	C ₂₇ H ₃₀ O ₁₆	3.8065E + 07	2.1896E + 07	3.5719E + 07	1.5513E + 07
27	3.46	Galloylpaeoniflorin	C ₃₀ H ₃₂ O ₁₅	1.3912E + 08	1.5200E + 08	1.1501E + 08	1.0863E + 08
28	3.47	Paeonolide	C ₂₀ H ₂₈ O ₁₂	1.0622E + 07	1.1936E + 07	9.1812E + 06	—
29	3.58	6-O-glucopyranosyl- lactinolide	C ₁₆ H ₂₆ O ₉	2.5249E + 08	2.3834E + 08	2.2675E + 08	2.1241E + 08
30	3.68	Oxypaeoniflorin	C ₂₃ H ₂₈ O ₁₂	1.5407E + 08	—	1.4345E + 08	1.3307E + 08
31	3.76	6-O-glucopyranosyl- lactinolide	C ₁₆ H ₂₆ O ₉	3.2664E + 08	—	3.0588E + 08	3.1627E + 08
32	3.88	Paeonilactone B	C ₁₀ H ₁₂ O ₄	9.0325E + 07	9.3539E + 07	5.1257E + 07	8.9597E + 07
33	3.93	Isomaltopaeoniflorin	C ₂₉ H ₃₈ O ₁₆	1.1545E + 10	1.1941E + 10	1.2282E + 10	9.4600E + 09
34	4.07	Albiflorin	C ₂₃ H ₂₈ O ₁₁	2.9587E + 10	2.9296E + 10	2.8430E + 10	2.8684E + 10
35	4.32	Glucopyranosylalbiflorin	C ₂₉ H ₃₈ O ₁₆	2.2813E + 09	2.4109E + 08	2.0383E + 08	1.6844E + 08
36	4.34	Galloylpaeoniflorin sulfonate	C ₃₀ H ₃₂ O ₁₇ S	7.6943E + 08	5.6793E + 08	1.5501E + 08	1.4886E + 09

TABLE 1: Continued.

No.	t_R (min)	Compound name	Formula	Paeoniae Radix Alba		Paeoniae Radix Alba-Atractylodis Macrocephalae Rhizoma herbal pair	
				(Measured area)		(Measured area)	
				Crude	Processed	Crude	Processed
37	4.34	Galloylpaeoniflorin isomer	$C_{30}H_{32}O_{15}$	$6.7592E + 08$	$7.4322E + 08$	$6.0470E + 08$	$5.4051E + 08$
38	4.38	1,2,3,6-tetra-O-galloylglucose	$C_{34}H_{28}O_{22}$	$4.6602E + 08$	$3.4977E + 08$	$4.0697E + 08$	$3.6901E + 08$
39	4.38	Tetragalloyl glucose A	$C_{34}H_{28}O_{22}$	$4.6602E + 08$	$3.4977E + 08$	$4.0697E + 08$	$3.6901E + 08$
40	4.56	Mudanpioside F	$C_{16}H_{24}O_8$	$8.4156E + 07$	$8.2734E + 07$	$7.2666E + 07$	$7.9227E + 07$
41	4.60	Oxypaeoniflorin isomer	$C_{23}H_{28}O_{12}$	$9.6610E + 08$	$9.8706E + 08$	$9.2464E + 08$	$8.7359E + 08$
42	4.65	Gallotannin	$C_{27}H_{24}O_{18}$	$6.7737E + 07$	—	—	—
43	4.77	Paeoniflorin	$C_{23}H_{28}O_{11}$	$5.9556E + 10$	$6.1356E + 10$	$5.9929E + 10$	$5.8832E + 10$
44	4.89	Paeoniflorin sulfonate II	$C_{23}H_{28}O_{13}S$	$1.1095E + 08$	$1.4567E + 08$	$5.5052E + 07$	$2.7813E + 08$
45	4.98	Isogalloylpaeoniflorin sulfonate	$C_{30}H_{32}O_{17}S$	$3.6742E + 07$	—	—	—
46	5.05	Ethyl gallate	$C_9H_{10}O_5$	$6.0669E + 07$	$5.4850E + 07$	$1.6681E + 07$	$2.6790E + 07$
47	5.05	Methyl salicylate	$C_8H_8O_3$	$6.0669E + 07$	$5.4850E + 07$	$1.6681E + 07$	$2.6790E + 07$
48	5.15	Benzoic acid	$C_7H_6O_2$	$4.0163E + 07$	$4.5493E + 07$	$2.9695E + 07$	$2.9727E + 07$
49	5.25	Paeonol	$C_9H_{10}O_3$	$6.8567E + 07$	$7.4129E + 07$	$9.9992E + 07$	$6.5619E + 07$
50	5.25	4-hydroxy-3-methoxy acetophenone	$C_9H_{10}O_3$	$6.8567E + 07$	$7.4129E + 07$	$9.9992E + 07$	$6.5619E + 07$
51	5.31	ortho-oxypaeoniflorin	$C_{23}H_{28}O_{12}$	$1.9080E + 09$	$1.9263E + 09$	$1.8723E + 09$	$1.6842E + 09$
52	5.63	Ethyl gallate	$C_9H_{10}O_5$	$1.4627E + 08$	$1.2812E + 08$	$1.0365E + 08$	$8.8155E + 07$
53	5.63	Methyl salicylate	$C_8H_8O_3$	$1.4627E + 08$	$1.2812E + 08$	$1.0365E + 08$	$8.8155E + 07$
54	5.66	Kaempferol-3-O-glucoside	$C_{21}H_{20}O_{11}$	$1.6012E + 07$	$1.7385E + 07$	—	—
55	5.66	Astragalin	$C_{21}H_{20}O_{11}$	$1.6012E + 07$	$1.7385E + 07$	—	—
56	6.01	Eugeniin	$C_{41}H_{30}O_{26}$	$2.7483E + 08$	$3.0279E + 08$	$2.8080E + 08$	$3.0479E + 08$
57	6.01	Dihydroxymethyl benzoyl tetragalloyl glucose	$C_{41}H_{30}O_{26}$	$2.7483E + 08$	$3.0279E + 08$	$2.8080E + 08$	$3.0479E + 08$
58	6.03	1,2,3,6-tetra-O-galloylglucose isomer A	$C_{34}H_{28}O_{22}$	$1.3555E + 09$	—	$1.1980E + 09$	$1.1039E + 09$
59	6.03	Tetragalloyl glucose B	$C_{34}H_{28}O_{22}$	$1.3555E + 09$	—	—	—
60	6.08	Astragalin	$C_{21}H_{20}O_{11}$	$1.5009E + 07$	$1.8552E + 07$	$1.5922E + 07$	$1.4002E + 07$
61	6.09	Isomaltopaeoniflorin isomer	$C_{29}H_{38}O_{16}$	$7.5172E + 07$	—	—	—
62	6.47	1,2,3,6-tetra-O-galloylglucose isomer B	$C_{34}H_{28}O_{22}$	$1.5882E + 09$	—	—	$1.2570E + 09$
63	6.47	Tetragalloyl glucose C	$C_{34}H_{28}O_{22}$	$1.5882E + 09$	—	—	$1.2570E + 09$
64	6.85	3,6-di-O-galloyl paeoniorin	$C_{37}H_{36}O_{19}$	$7.6512E + 07$	—	—	—
65	6.96	1,2,3,6-tetra-O-galloylglucose	$C_{34}H_{28}O_{22}$	$4.4729E + 08$	$4.5825E + 08$	$4.0642E + 08$	$4.2393E + 08$
66	6.96	Tetragalloyl glucose D	$C_{34}H_{28}O_{22}$	$4.4729E + 08$	$4.5825E + 08$	$4.0642E + 08$	$4.2393E + 08$
67	7.35	Galloylpaeoniflorin isomer I	$C_{30}H_{32}O_{15}$	$1.2156E + 10$	$1.2451E + 10$	$1.1484E + 10$	$1.0962E + 10$
68	7.60	1-O-glucopyranosyl-8-O-benzoyl paenonisfrone	$C_{23}H_{28}O_{10}$	$4.3983E + 07$	$4.5347E + 07$	$4.4927E + 07$	$3.9869E + 07$
69	7.71	Glucopyranosylalbiorin isomer I	$C_{29}H_{38}O_{16}$	$7.2982E + 07$	$7.9341E + 07$	—	$1.8872E + 07$

TABLE 1: Continued.

No.	t_R (min)	Compound name	Formula	Paeoniae Radix Alba		Paeoniae Radix Alba-Atractylodis Macrocephalae Rhizoma herbal pair	
				(Measured area)		(Measured area)	
				Crude	Processed	Crude	Processed
70	8.18	1-O-glucopyranosyl-8-O-benzoyl paeonisuffrone	$C_{23}H_{28}O_{10}$	$7.4648E + 07$	$8.3204E + 07$	$6.5957E + 07$	$5.9832E + 07$
71	8.31	Ortho-oxypaeoniflorin	$C_{23}H_{28}O_{12}$	$2.4469E + 07$	$2.4504E + 07$	$2.3932E + 07$	$2.2796E + 07$
72	8.45	1,2,3,4,6-Penta-O-galloyl-D-glucopyranose	$C_{41}H_{32}O_{26}$	$1.1843E + 10$	$1.0905E + 10$	$1.0518E + 10$	$1.0489E + 10$
73	8.45	Pentagalloyl glucose	$C_{41}H_{32}O_{26}$	$1.1843E + 10$	$1.0905E + 10$	$1.0518E + 10$	$1.0489E + 10$
74	8.64	Lactiflorin	$C_{23}H_{26}O_{10}$	$1.0818E + 08$	$1.8628E + 08$	$1.3689E + 08$	—
75	8.80	Galloylalbiroin	$C_{30}H_{32}O_{15}$	$3.2696E + 09$	—	—	—
76	9.17	Astragalin	$C_{21}H_{20}O_{11}$	$1.0717E + 07$	$1.3960E + 07$	$1.2843E + 07$	$1.0582E + 07$
77	9.25	Lactinolide	$C_{10}H_{16}O_4$	$2.7251E + 07$	$2.6105E + 07$	$2.1735E + 07$	$3.2770E + 07$
78	9.29	Galloylpaeoniflorin isomer II	$C_{30}H_{32}O_{15}$	$2.8831E + 09$	—	$2.6829E + 09$	$2.2850E + 09$
79	9.68	Glucopyranosylalbiorin isomer II	$C_{29}H_{38}O_{16}$	$2.4321E + 07$	$2.6804E + 07$	$2.2576E + 07$	$2.4950E + 07$
80	9.84	Hexagalloyl glucose	$C_{48}H_{36}O_{30}$	$4.9153E + 07$	—	$6.8676E + 08$	$5.7793E + 08$
81	9.95	Oxybenzoyl-oxypaeoniflorin	$C_{30}H_{32}O_{14}$	$1.4385E + 07$	$1.6654E + 07$	$1.1051E + 07$	$1.1345E + 07$
82	10.07	1-O-glucopyranosyl-8-O-benzoylpaeonisuffrone	$C_{23}H_{28}O_{10}$	$3.6916E + 09$	$3.5634E + 09$	$3.1333E + 09$	$3.2106E + 09$
83	10.29	Albiflorin R1 isomer I	$C_{23}H_{28}O_{11}$	$6.3346E + 09$	$6.6205E + 09$	$5.9528E + 09$	$5.8736E + 09$
84	10.74	Hexagalloyl glucose	$C_{48}H_{36}O_{30}$	$4.9225E + 08$	$2.5582E + 08$	$1.9395E + 09$	$1.5439E + 09$
85	10.76	Lactiflorin	$C_{23}H_{26}O_{10}$	$1.2785E + 09$	$3.5174E + 09$	$9.9713E + 08$	$3.4524E + 09$
86	10.84	Benzoylpaeoniflorin Sulfonate	$C_{30}H_{32}O_{14}S$	$9.0616E + 08$	$6.4075E + 08$	$1.5946E + 08$	$2.1931E + 09$
87	10.88	3,6-di-O-galloyl paeoniorin	$C_{37}H_{36}O_{19}$	$1.6123E + 08$	—	—	—
88	10.95	Ortho-oxypaeoniflorin isomer	$C_{23}H_{28}O_{12}$	$5.5563E + 07$	$5.8774E + 07$	$5.7147E + 07$	$5.6640E + 07$
89	11.52	3,6-di-O-galloyl paeoniorin	$C_{37}H_{36}O_{19}$	$3.6509E + 08$	$3.9290E + 08$	$5.2162E + 08$	$5.3781E + 08$
90	11.72	3,6-di-O-galloyl paeoniorin isomer	$C_{37}H_{36}O_{19}$	$9.7356E + 08$	—	$1.2523E + 09$	$9.5929E + 08$
91	11.75	Galloylalbiroin isomer I	$C_{30}H_{32}O_{15}$	$2.3457E + 08$	—	—	—
92	11.84	Oxypaeoniflorin sulfonate isomer	$C_{23}H_{28}O_{14}S$	$2.1063E + 07$	$1.9747E + 07$	$1.3875E + 07$	$1.0840E + 07$
93	12.15	1-O-glucopyranosyl-8-O-benzoylpaeonisuffrone	$C_{23}H_{28}O_{10}$	$7.2104E + 07$	$7.1468E + 07$	$6.7309E + 07$	$6.5917E + 07$
94	12.15	Oxybenzoyl-oxypaeoniflorin	$C_{30}H_{32}O_{14}$	$1.9982E + 08$	—	—	$1.6891E + 08$
95	12.18	Benzoyloxyppaeoniflorin	$C_{30}H_{32}O_{13}$	$2.0822E + 08$	—	$2.0163E + 08$	$1.9074E + 08$
96	13.42	Benzoyloxyppaeoniflorin isomer	$C_{30}H_{32}O_{13}$	$8.6458E + 07$	$6.2282E + 07$	$7.6048E + 07$	$7.2791E + 07$
97	13.44	Oxybenzoyl-oxypaeoniflorin isomer I	$C_{30}H_{32}O_{14}$	$1.4728E + 07$	$1.7389E + 07$	$1.5360E + 07$	$1.6008E + 07$
98	13.85	Galloylalbiroin isomer II	$C_{30}H_{32}O_{15}$	$9.6403E + 07$	$1.2196E + 08$	$1.0506E + 08$	$1.0272E + 08$
99	14.05	Oxybenzoyl-oxypaeoniflorin isomer II	$C_{30}H_{32}O_{14}$	$2.5323E + 07$	$2.9603E + 07$	$2.3556E + 07$	$2.8526E + 07$
100	14.13	Benzoyloxyppaeoniflorin	$C_{30}H_{32}O_{13}$	$3.8096E + 07$	$3.8557E + 07$	$3.7499E + 07$	$3.5800E + 07$

TABLE 1: Continued.

No.	t_R (min)	Compound name	Formula	Paeoniae Radix Alba		Paeoniae Radix Alba-Atractylodis Macrocephalae Rhizoma herbal pair	
				(Measured area)		(Measured area)	
				Crude	Processed	Crude	Processed
101	15.07	Benzoyloxyppaeoniflorin isomer I	$C_{30}H_{32}O_{13}$	$1.9827E + 07$	$2.3616E + 07$	—	—
102	15.38	Benzoyloxyppaeoniflorin isomer II	$C_{30}H_{32}O_{13}$	$1.1841E + 07$	$1.3730E + 07$	—	—
103	16.01	Oxybenzoyl-paeoniflorin	$C_{30}H_{32}O_{12}$	$1.8152E + 07$	—	$1.8435E + 07$	—
104	16.95	Isobenzoylpaeoniflorin	$C_{30}H_{32}O_{12}$	$1.2225E + 10$	$1.3228E + 10$	$1.2158E + 10$	$1.2391E + 10$
105	16.95	Oxybenzoyl-paeoniflorin isomer I	$C_{30}H_{32}O_{12}$	$1.2225E + 10$	$1.3228E + 10$	$1.2158E + 10$	$1.2391E + 10$
106	17.23	Benzoylpaeoniflorin Sulfonate	$C_{30}H_{32}O_{14}S$	$1.5680E + 07$	$1.2235E + 07$	$5.6573E + 06$	$3.5831E + 07$
107	17.48	Isobenzoylpaeoniflorin isomer I	$C_{30}H_{32}O_{12}$	$5.4138E + 09$	$5.4432E + 09$	$5.2522E + 09$	$5.3238E + 09$
108	17.48	Oxybenzoyl-paeoniflorin isomer II	$C_{30}H_{32}O_{12}$	$5.4138E + 09$	$5.4432E + 09$	$5.2522E + 09$	$5.3238E + 09$
109	17.86	Benzoyloxyppaeoniflorin	$C_{30}H_{32}O_{13}$	$3.4347E + 07$	$3.4852E + 07$	$3.5980E + 07$	$3.8814E + 07$
110	18.55	Benzoyloxyppaeoniflorin isomer	$C_{30}H_{32}O_{13}$	$1.5397E + 07$	$1.7656E + 07$	$1.7246E + 07$	$1.8012E + 07$
111	18.69	Albiflorin R1 isomer II	$C_{23}H_{28}O_{11}$	$2.0046E + 07$	$1.9851E + 07$	$2.3462E + 07$	—
112	19.30	Albiflorin R1 isomer III	$C_{23}H_{28}O_{11}$	$2.9827E + 06$	—	—	$5.6105E + 06$
113	21.79	Palbinone	$C_{22}H_{30}O_4$	$8.9687E + 07$	$1.3174E + 08$	$1.2834E + 08$	$5.7610E + 07$
114	21.93	Isobenzoylpaeoniflorin isomer II	$C_{30}H_{32}O_{12}$	$4.5356E + 08$	$4.2874E + 07$	$3.4016E + 08$	$2.7347E + 08$
115	21.93	Oxybenzoyl-paeoniflorin isomer III	$C_{30}H_{32}O_{12}$	$4.5356E + 08$	$4.2874E + 07$	$3.4016E + 08$	$2.7347E + 08$
116	22.15	Paeonilactinone	$C_{10}H_{16}O_2$	$7.0423E + 06$	$3.7108E + 06$	$8.0036E + 06$	$6.6886E + 06$
117	36.46	Hederagenin	$C_{30}H_{48}O_4$	$7.6725E + 07$	$8.1456E + 07$	$9.7498E + 07$	$4.7332E + 07$
118	37.31	23-hydroxybetulinic acid	$C_{30}H_{48}O_4$	$3.9836E + 07$	$4.0995E + 07$	$3.9906E + 07$	$2.2611E + 07$
119	38.14	Astrantiagenin D	$C_{30}H_{46}O_4$	$7.8714E + 06$	$7.9560E + 06$	$1.1904E + 07$	$3.8958E + 06$
120	43.00	Astrantiagenin D isomer	$C_{30}H_{46}O_4$	$4.0450E + 06$	—	$3.1585E + 06$	—
121	45.65	Oleanolic acid	$C_{30}H_{48}O_3$	$1.1266E + 08$	$9.4258E + 07$	$7.6434E + 07$	$4.3295E + 07$
122	46.10	Betulinic acid	$C_{30}H_{48}O_3$	$6.2494E + 06$	$2.3289E + 07$	$4.0543E + 07$	$2.3912E + 07$
123	52.48	Daucosterol	$C_{35}H_{60}O_6$	$1.4060E + 07$	$1.9624E + 07$	$8.5440E + 06$	$6.3156E + 06$

Paeoniae Radix Alba-Atractylodis Macrocephalae Rhizoma herbal pair frequently used in all China dynasties [6, 7]. Paeoniae Radix Alba nourishes blood and liver, and Atractylodis Macrocephalae Rhizoma helps invigorate spleen and eliminate dampness [8–12]. Thus, the compatibility of these two medicines could help achieve the goal of purging wood from the earth, regulating the functions of liver and spleen, benefiting *qi*, and nourishing blood [13–15]. Although the compositions of these two medicines have been extensively studied, the appropriate processing method of them, such as frying, which is believed by the practitioners of traditional medicine to have the effects for enhancing the efficacy of the medicine, and their underlying compatibility mechanism are still under investigation.

The objective of this study is to investigate the qualitative, preprocessing, and postprocessing changes in the composition and compatibility of Paeoniae Radix Alba and Atractylodis Macrocephalae Rhizoma by using Q Exactive hybrid quadrupole-Orbitrap mass spectrometer combined with high-performance quadrupole precursor selection with high-resolution and accurate-mass Orbitrap detection. The work could serve as a theoretical basis for the development of medicines from Paeoniae Radix Alba and Atractylodis Macrocephalae Rhizoma, and the reasonable clinical medication. Furthermore, it provides new insights into the investigation of the herbal pair and for the study of the appropriate processing method for Chinese herbal medicines and their underlying compatibility mechanism.

TABLE 2: Major chemical constituents identified in crude and processed *Atractylodis Macrocephalae Rhizoma* and in crude and processed *Paeoniae Radix Alba-Atractylodis Macrocephalae Rhizoma* herbal pair.

No.	t_R (min)	Compound name	Formula	Atractylodis Macrocephalae Rhizoma (Measured area)		Paeoniae Radix Alba-Atractylodis Macrocephalae Rhizoma herbal pair (Measured area)	
				Crude	Processed	Crude	Processed
1	1.72	Protocatechuic acid	C ₇ H ₆ O ₄	2.0389E + 07	1.4454E + 07	2.0881E + 07	2.4383E + 07
2	2.67	Protocatechuic acid isomer I	C ₇ H ₆ O ₄	9.6661E + 07	—	—	—
3	3.24	Caffeic acid	C ₉ H ₈ O ₄	3.6818E + 08	1.7393E + 08	2.8796E + 08	1.2882E + 08
4	3.73	Protocatechuic acid isomer II	C ₇ H ₆ O ₄	2.0846E + 07	—	—	1.2022E + 07
5	4.21	Dictamnoside A isomer I	C ₂₁ H ₃₆ O ₉	1.8843E + 07	2.4981E + 07	1.0636E + 07	1.3140E + 07
6	4.70	Dictamnoside A isomer II	C ₂₁ H ₃₆ O ₉	2.8770E + 07	3.4768E + 07	1.0395E + 07	1.4208E + 07
7	5.63	Scopoletin	C ₁₀ H ₈ O ₄	6.1458E + 07	4.1494E + 07	6.1562E + 07	5.3342E + 07
8	5.82	Dictamnoside A	C ₂₁ H ₃₆ O ₉	9.6195E + 07	1.1991E + 08	7.5446E + 07	9.4190E + 07
9	8.77	Atractylentriol	C ₁₄ H ₁₆ O ₃	1.2538E + 07	5.4052E + 06	—	—
10	9.33	Ferulic acid	C ₁₀ H ₁₀ O ₄	1.3958E + 07	9.1214E + 06	1.1912E + 07	9.6849E + 06
11	25.81	Atractylenolide I isomer	C ₁₅ H ₁₈ O ₂	4.5224E + 09	4.2401E + 09	5.9401E + 09	6.5277E + 09
12	25.83	Atractylenolide III	C ₁₅ H ₂₀ O ₃	2.5549E + 09	1.8023E + 09	2.8280E + 09	3.1632E + 09
13	26.17	12-methylbutyryl-14-acetyl-2E,8EZ,10E-atractylentriol	C ₂₁ H ₂₆ O ₅	2.4755E + 07	—	—	—
14	26.95	12-methylbutyryl-14-acetyl-2E,8EZ,10E-atractylentriol isomer	C ₂₁ H ₂₆ O ₅	7.5991E + 07	—	—	—
15	31.10	Atractylenolide II isomer	C ₁₅ H ₂₀ O ₂	6.7883E + 09	4.5794E + 09	7.6246E + 09	7.8814E + 09
16	31.66	Atractylenolide II	C ₁₅ H ₂₀ O ₂	2.8279E + 10	1.9902E + 10	3.0285E + 10	3.1294E + 10
17	33.44	Atractyldin	C ₁₃ H ₁₀ O	6.4157E + 06	—	7.0452E + 07	—
18	35.07	Atractylenolide I isomer	C ₁₅ H ₁₈ O ₂	8.2226E + 08	1.4781E + 09	1.0831E + 09	3.2083E + 09
19	35.94	Atractylenolide I	C ₁₅ H ₁₈ O ₂	8.8877E + 09	7.2520E + 09	8.3857E + 09	1.2742E + 10
20	39.03	12-methylbutyryl-14-acetyl-2E,8EZ,10E-atractylentriol isomer I	C ₂₁ H ₂₆ O ₅	3.0978E + 07	3.7863E + 07	2.9171E + 07	—
21	39.81	Dibutyl phthalate	C ₁₆ H ₂₂ O ₄	1.1372E + 08	9.8325E + 07	1.2659E + 08	1.4865E + 08
22	40.00	12-methylbutyryl-14-acetyl-2E,8EZ,10E-atractylentriol isomer II	C ₂₁ H ₂₆ O ₅	3.8810E + 07	7.7498E + 07	3.3885E + 07	7.0522E + 07
23	40.26	Dibutyl phthalate isomer	C ₁₆ H ₂₂ O ₄	1.0631E + 08	5.4902E + 07	6.1958E + 07	4.6227E + 07
24	41.50	14-methylbutyryl-2E,8EZ,10Es-atractylentriol	C ₁₉ H ₂₄ O ₄	4.9587E + 07	2.8423E + 07	5.1146E + 07	4.7855E + 07
25	46.43	Spinasteryl	C ₂₉ H ₄₈ O	8.6778E + 06	7.9096E + 06	1.0609E + 07	7.7832E + 06
26	47.32	Atractylon	C ₁₅ H ₂₀ O	7.4433E + 07	5.4063E + 07	6.6146E + 07	—
27	47.37	Biatractylolide	C ₃₀ H ₃₈ O ₄	1.0949E + 09	9.5665E + 08	1.2797E + 09	—
28	47.96	Linoleic acid	C ₁₈ H ₃₂ O ₂	1.8499E + 08	1.5041E + 08	1.8777E + 08	2.3743E + 08
29	48.25	Linoleic acid isomer	C ₁₈ H ₃₂ O ₂	2.1059E + 07	—	—	—
30	48.59	Biepiasterolid isomer	C ₃₀ H ₃₈ O ₄	9.0255E + 08	7.0863E + 08	7.4011E + 08	—
31	48.90	Atractylon isomer	C ₁₅ H ₂₀ O	9.5308E + 07	8.7683E + 07	8.2967E + 07	1.0132E + 08
32	49.42	Palmitic acid	C ₁₆ H ₃₂ O ₂	2.2356E + 07	2.2942E + 07	2.5949E + 07	2.0153E + 07

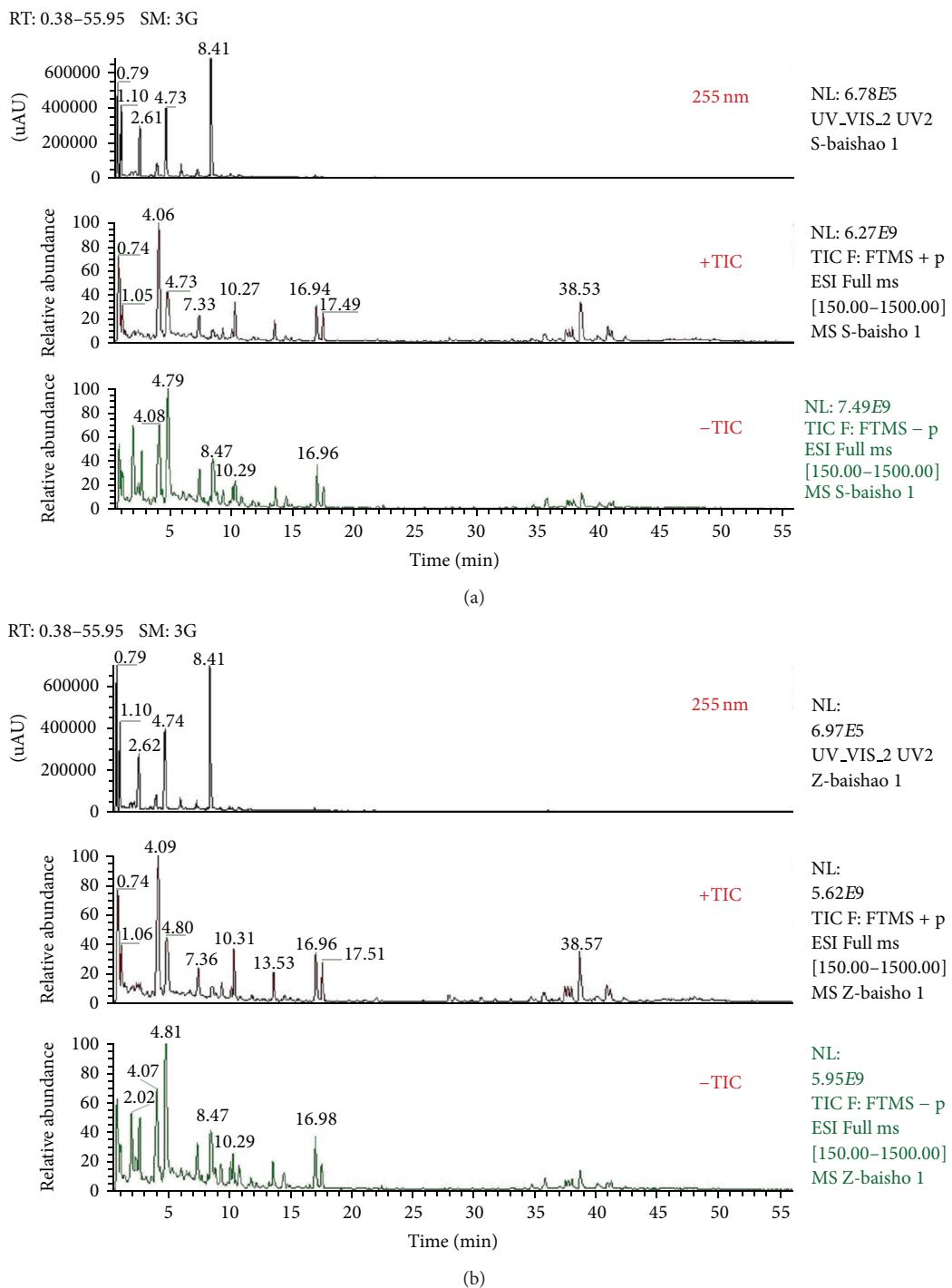


FIGURE 1: Total ion chromatograms of crude (a) and processed (b) *Paeoniae Radix Alba* obtained from both positive and negative ion modes.

2. Experimental

2.1. Chemicals, Solvents, and Herbal Materials. *Paeoniae Radix Alba* and *Atractylodis Macrocephalae Rhizoma* samples were acquired from Zhejiang suppliers. All of these herbal samples were authenticated by Professor Jianwei Chen (College of Pharmacy, Nanjing University of Chinese Medicine). HPLC-grade acetonitrile and formic acid were obtained from Merck (Darmstadt, Germany). Deionized

water was purified using the Milli-Q system (Millipore, Bedford, MA, USA). All other reagents and chemicals were analytical grade.

2.2. Preparation of the Sample Solutions. The dried and powdered samples of crude and processed *Paeoniae Radix Alba*, crude and processed *Atractylodis Macrocephalae Rhizoma*, and their crude and processed herbal pair extracts (1:1, g/g)

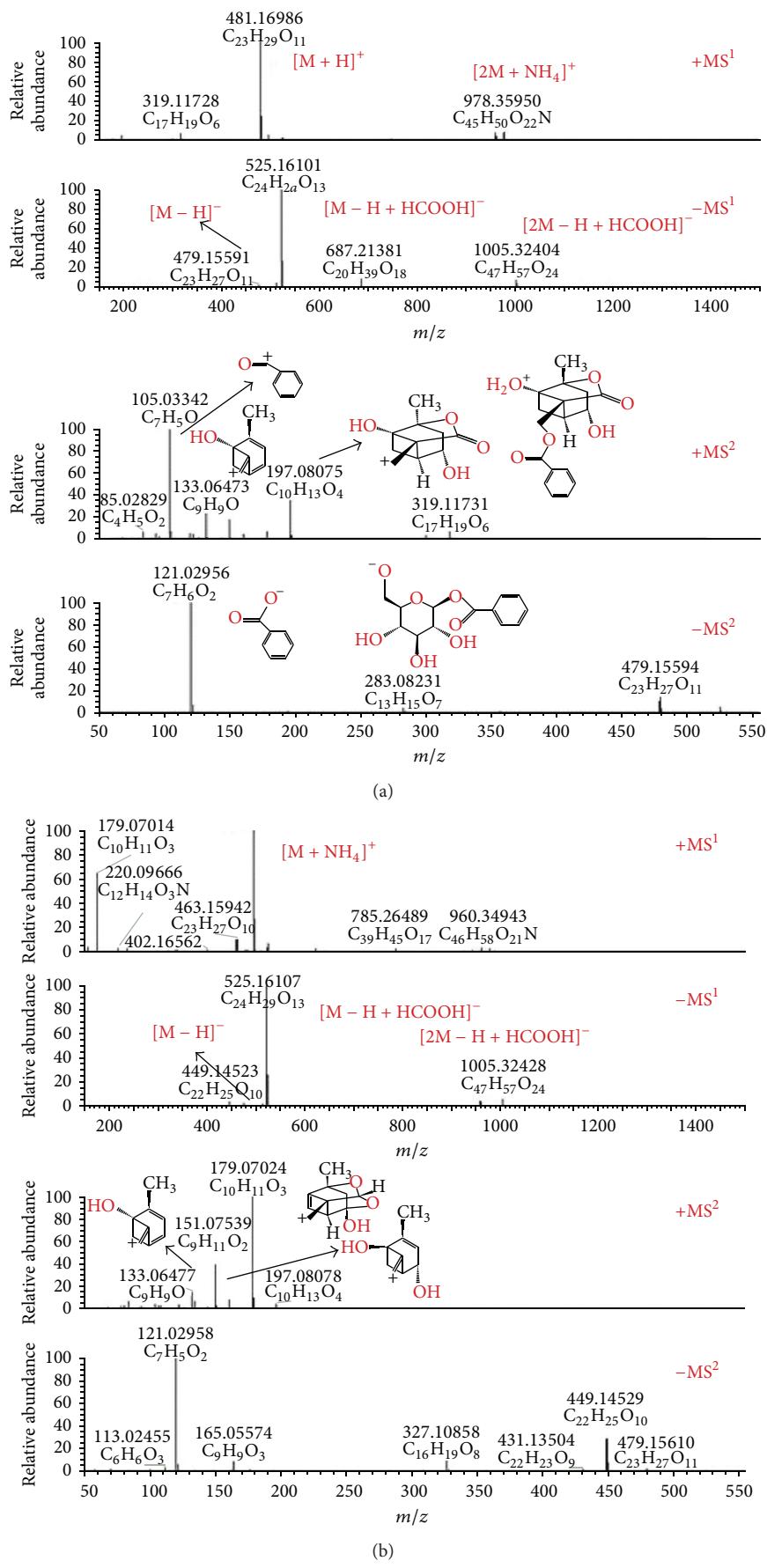


FIGURE 2: Continued.

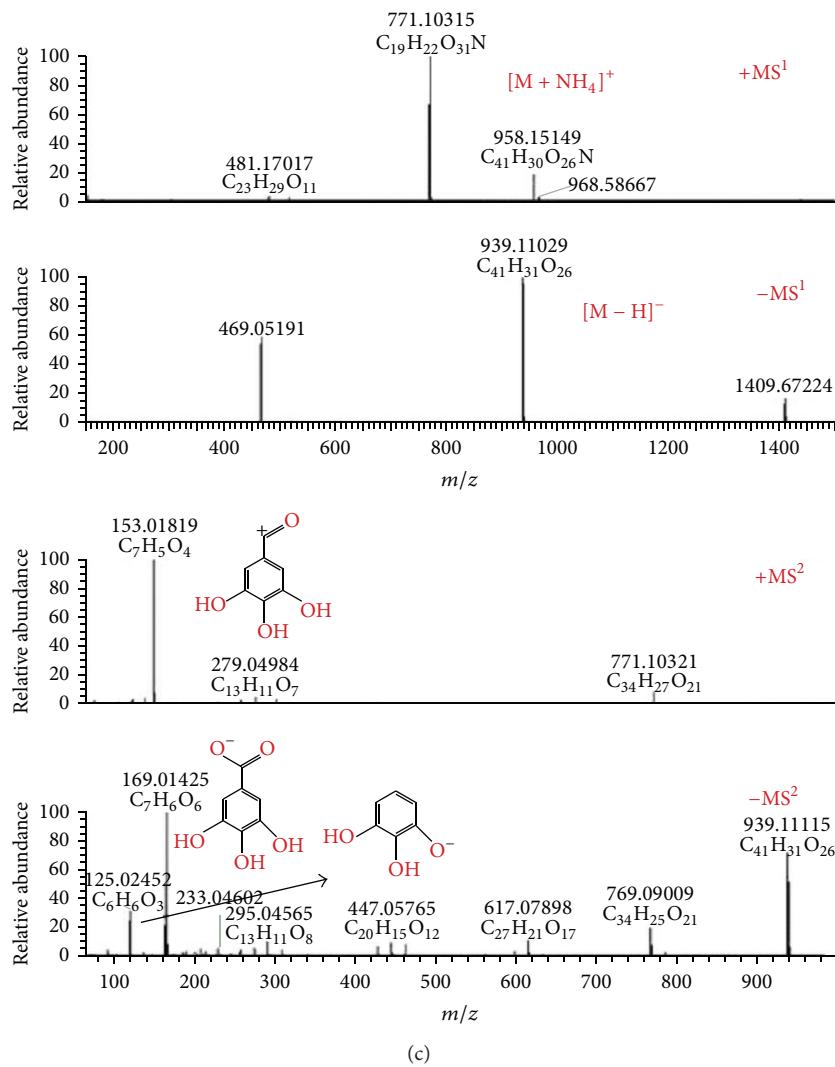


FIGURE 2: Mass spectra and proposed fragmentations of albiflorin (a), paeoniflorin (b), and 1,2,3,4,6-penta-O-galloyl-beta-D-glucopyranose (c).

were prepared. A total of 2.0 g of each sample powder was accurately weighed and transferred into a 50 mL round bottom flask with 20 mL of 70% methanol aqueous solution (v/v) and refluxed in a 80°C water bath for 1 h. The filtrate was collected after filtration and the residue was then refluxed with 20 mL of 70% methanol aqueous solution in a 80°C water bath for 1 h, the filtrate was collected again after filtration and the residue was removed. Finally, the combined filtrates were treated by rotary evaporation concentration and the resultant residue was dissolved and transferred into a 25 mL volumetric flask with 70% methanol aqueous solution to make it up to a final concentration of 0.08 g·mL⁻¹. All solutions were stored at 4°C and filtered through a 0.22 μm filter membrane before injection into the HPLC system.

2.3. Liquid Chromatography and Mass Spectrometry. Analyses were performed by using Dionex UltiMate 3000 HPLC system (Dionex, Sunnyvale, CA, USA) with a diode array detector. Detection wavelengths were set at

255 nm. A Thermo Scientific Hypersil Gold C₁₈ column (100 mm × 2.1 mm, 1.9 μm) was used with a flow rate of 0.35 mL·min⁻¹. The injection volume was 5 μL, and the column temperature was maintained at 30°C. The sample separation was performed according to the previous reports with minor modification [16–18]. The mobile phase was composed of (a) aqueous formic acid (0.1%, v/v) and (b) acetonitrile under following gradient elution: 10–55% B from 0 to 40 min, 55–90% B from 40 to 51 min, 90% B from 51 to 56 min, 90–10% B from 56 to 56.1 min, and 10% B from 56.1 to 60 min. Mass spectrometry was performed on a Q Exactive high-resolution benchtop quadrupole Orbitrap mass spectrometer (Thermo Fisher Scientific, San Jose, USA) using a heated electrospray ionization (HESI-II) source for ionization of the target compounds in positive and negative ion modes. The key parameters were as follows: ionization voltage, +3.0 kV/-2.8 kV; sheath gas pressure, 35 arbitrary units; auxiliary gas, 10 arbitrary units; heat temperature, 300°C; and capillary temperature, 300°C. For

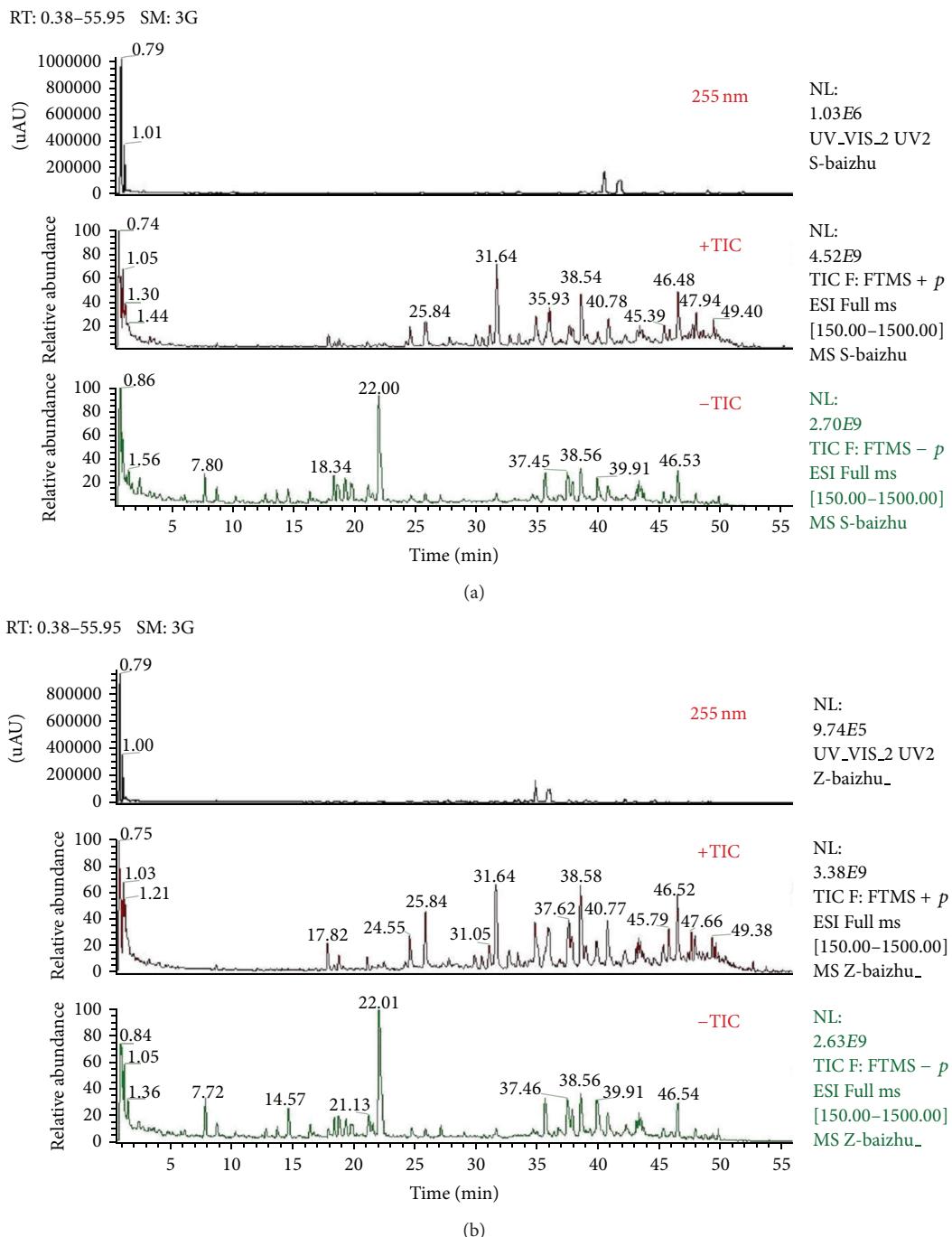


FIGURE 3: Total ion chromatograms of crude (a) and processed (b) *Atractylodis Macrocephala Rhizoma* obtained from both positive and negative ion modes.

the compounds of interest, a scan range of m/z 150–1500 was chosen. Resolution for higher energy collisional dissociation cell (HCD) spectra was set to 17,500 at m/z 150 on the Q Exactive.

3. Results and Discussion

3.1. Identification of the Main Components in Crude and Processed *Paeoniae Radix Alba*.

Tentative identification of the main compounds in crude and processed *Paeoniae Radix Alba* samples was generated based on elemental composition data determined from accurate mass measurements and comparison with the literature data. The total ion chromatograms of crude and processed *Paeoniae Radix Alba* samples obtained from both positive and negative ion modes were shown in Figure 1. In the preliminary study, the Q Exactive mass spectrometer was confirmed to be highly selective and sensitive. Under the present chromatographic and MS

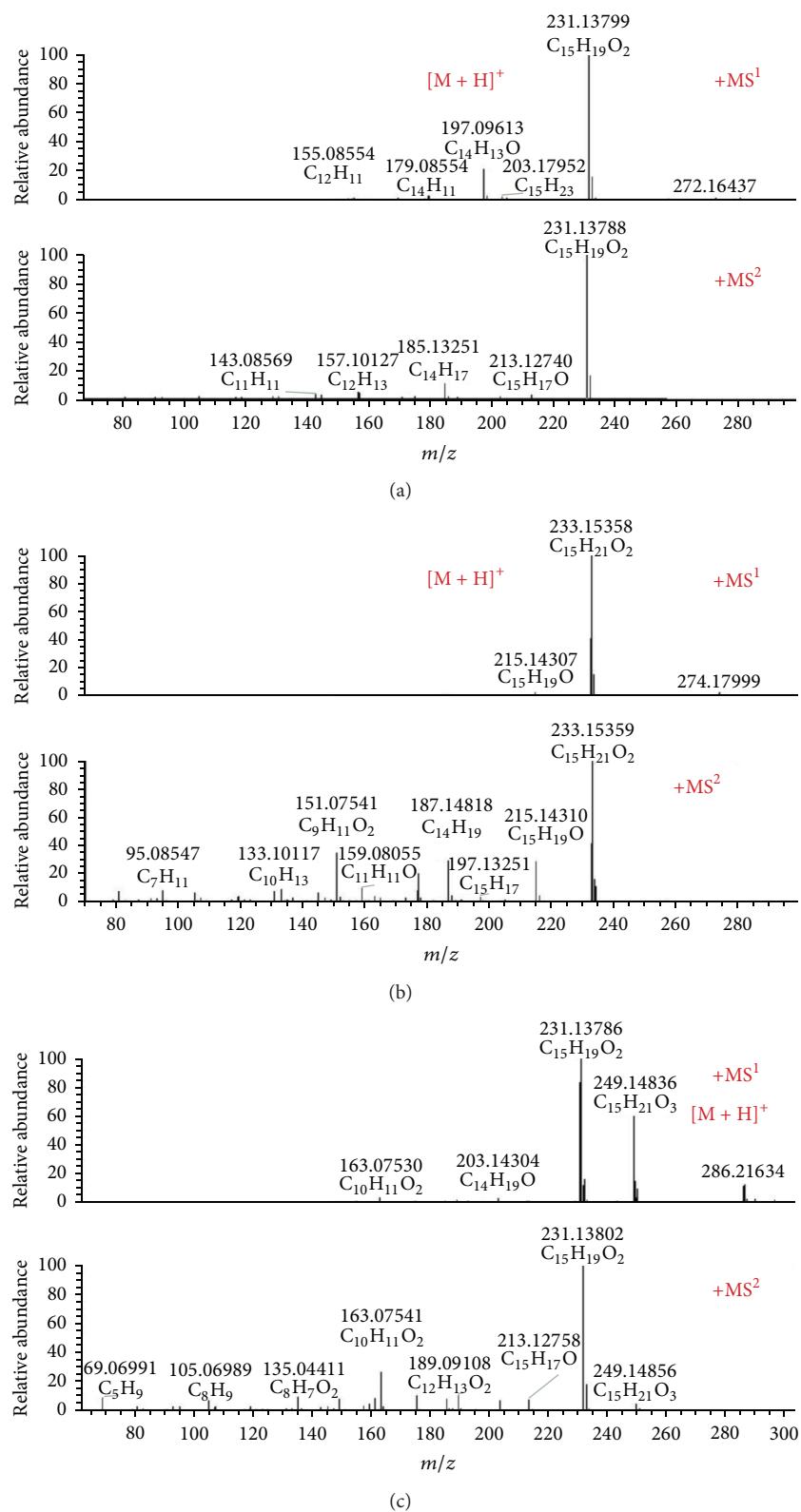


FIGURE 4: Mass spectra of atracylenolide I (a), atracylenolide II (b), and atracylenolide III (c).

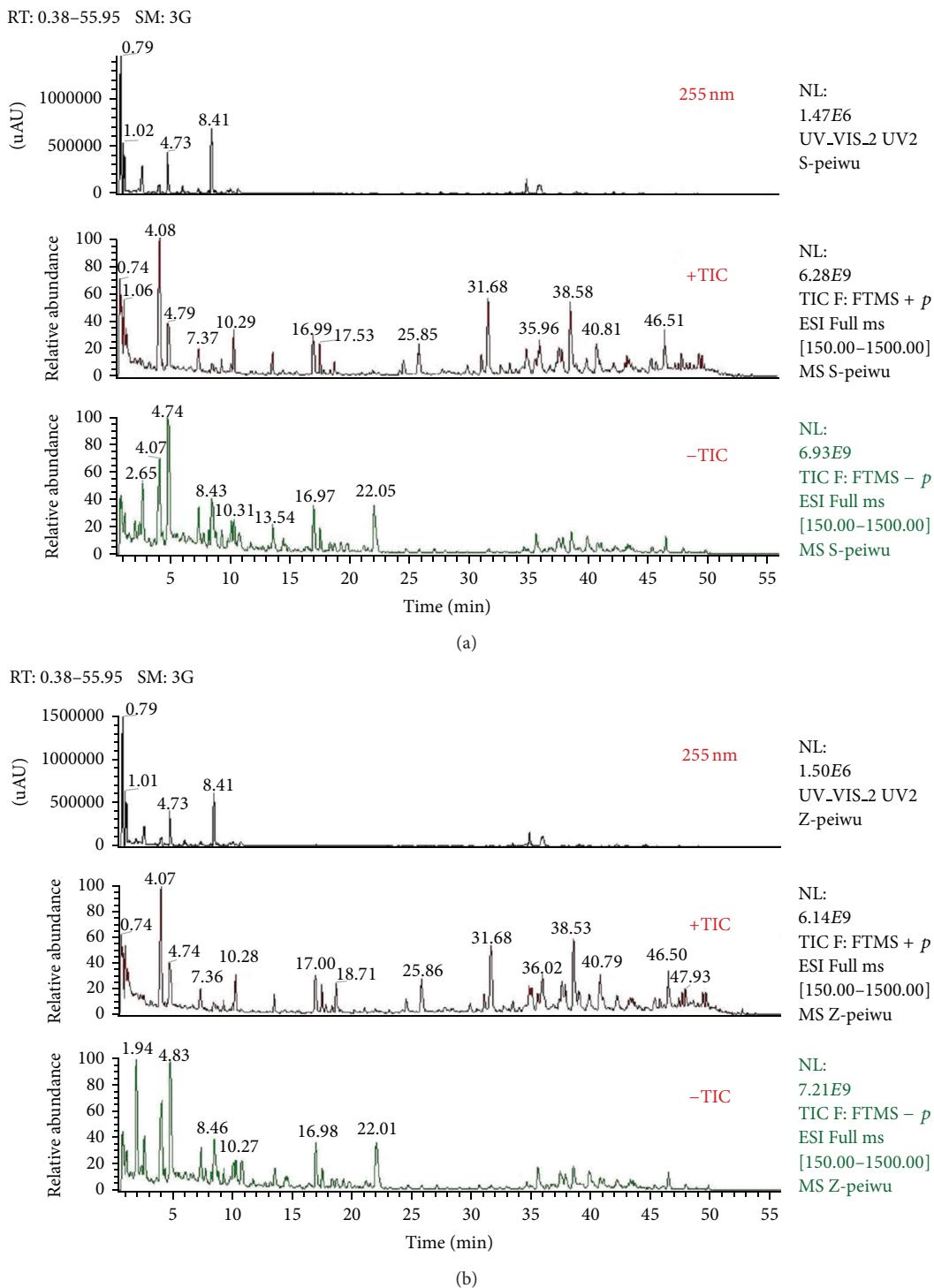


FIGURE 5: Total ion chromatograms of crude (a) and processed (b) Paeoniae Radix Alba-Atractylodis Macrocephalae Rhizoma herbal pair obtained from both positive and negative ion modes.

conditions, 123 and 101 compounds were identified in crude and processed Paeoniae Radix Alba samples, respectively. Compounds 16, 30, 31, 42, 45, 58, 59, 61, 62, 63, 64, 75, 78, 80, 87, 90, 91, 94, 95, 103, 112, and 120 were not detected in processed Paeoniae Radix Alba sample. Meanwhile, the ESI-MS data of crude and processed samples demonstrated

that the peak areas of components 8, 113, and 122 varied significantly, and their amounts were dramatically increased in processed sample. The results were shown in Table 1.

From ESI-MS information, it was found that the sensitivities for all kinds of components in Paeoniae Radix Alba were high in both positive and negative ion modes.

In present study, we chose peaks 1, 2, and 3 to explain the identification process using Q Exactive high-performance benchtop quadrupole-Orbitrap LC-MS/MS. Peaks 1, 2, and 3 were eluted at retention times of 4.08, 4.79, and 8.47 min, respectively. Peak 1 showed the $[M+H]^+$ m/z 481.16986, $[2M+NH_4]^+$ m/z 978.35950, $[M-H]^-$ m/z 479.15591, $[M-H+HCOOH]^-$ m/z 525.16101, and $[2M-H+HCOOH]^-$ m/z 1005.32404 and the corresponding elemental compositions were $C_{23}H_{29}O_{11}$, $C_{46}H_{60}O_{22}N$, $C_{23}H_{27}O_{11}$, $C_{24}H_{29}O_{13}$, and $C_{47}H_{57}O_{24}$, respectively. On the basis of above data we deduced that the elemental composition of peak 1 was $C_{23}H_{28}O_{11}$. The molecular ion of peak 1 could lead to seven main MS^2 ions at m/z 319.11731, 197.08075, 133.06473, and 105.03342 in positive ion mode, and m/z 479.15594, 283.08231, and 121.02956 in negative ion mode. On the basis of the elemental compositions of fragment ions, peak 1 was assigned as albiflorin. Peaks 2 and 3 were therefore identified as paeoniflorin, and 1, 2, 3, 4, 6-penta-O-galloyl-beta-D-glucopyranose with above mentioned method. The mass spectra and proposed fragmentations of albiflorin, paeoniflorin, and 1, 2, 3, 4, 6-penta-O-galloyl-beta-D-glucopyranose were shown in Figure 2.

3.2. Identification of the Main Components in Crude and Processed Atractylodis Macrocephalae Rhizoma. Figure 3 showed the total ion chromatograms of crude and processed Atractylodis Macrocephalae Rhizoma samples obtained from both positive and negative ion modes. 32 and 26 compounds were identified in crude and processed Atractylodis Macrocephalae Rhizoma samples, respectively. Compounds 2, 4, 13, 14, 17, and 29 were not detected in processed Atractylodis Macrocephalae Rhizoma sample. Moreover, the amounts of compounds 3, 7, 9, 10, 21, 23, and 27 were substantially decreased, and the amounts of compounds 8, 18, and 22 were increased in processed sample compared with crude one. The results were shown in Table 2.

Atractylenolide I, atractylenolide II, and atractylenolide III are the main active compounds that belong to the sesquiterpenes in Atractylodis Macrocephalae Rhizoma. The mass spectra of atractylenolide I showed a $[M+H]^+$ ion at m/z 231.13799, which could lead to four MS^2 ions at m/z 213.12740, 185.13251, 157.10127, and 143.08569. The molecular ion of atractylenolide II ($[M+H]^+$ m/z 233.15358) could lead to six MS^2 ions at m/z 215.14310, 187.14818, 159.08055, 151.07541, 133.10117, and 95.08547. Meanwhile, the MS^2 spectrum of m/z 249.14836 from atractylenolide III contained six major fragment ions at m/z 231.13802, 213.12758, 189.09108, 163.07541, 135.04411, and 105.06989. The mass spectra of the above three compounds were shown in Figure 4.

3.3. Analysis of Chemical Changes of Paeoniae Radix Alba after Compatibility with Atractylodis Macrocephalae Rhizoma. In the present study, the Q Exactive high-performance benchtop quadrupole-Orbitrap LC-MS/MS based on chemical profiling approach was used to evaluate chemical constitution between co-decoction and single decoction of Paeoniae Radix Alba and Atractylodis Macrocephalae Rhizoma. For crude Paeoniae Radix Alba, the relative contents of most

compounds were dramatically decreased except those of compounds 80, 90, 98, 113, 119, and 122 were significantly increased and 19 compounds were not detected after its compatibility with crude Atractylodis Macrocephalae Rhizoma. For processed Paeoniae Radix Alba, the relative contents of compounds 12, 36, 84, and 86 were remarkably increased except 12 compounds including pedunculagin, oxypaeoniflorin, 6-O-glucopyranosyl-lactinolide, 1, 2, 3, 6-tetra-O-galloylglucose isomer A, 1, 2, 3, 6-tetra-O-galloylglucose isomer B, tetragalloyl glucose C, galloylpaeoniflorin isomer II, hexagalloyl glucose, 3, 6-di-O-galloyl paeoniorin isomer, oxybenzoyl-oxypaeoniflorin, benzoyloxy paeoniflorin, and albiflorin R1 isomer III were newly generated and 13 compounds were not found after its compatibility with processed Atractylodis Macrocephalae Rhizoma. The results were presented in Figure 5 and Table 1.

3.4. Analysis of the Chemical Changes of Atractylodis Macrocephalae Rhizoma after Compatibility with Paeoniae Radix Alba. For crude Atractylodis Macrocephalae Rhizoma, the relative contents of compounds 17, 18, and 25 were increased clearly except those of compounds 6, 23, and 30 decreased considerably and six compounds including protocatechuic acid isomer I, protocatechuic acid isomer II, atracylentriol, 12-methylbutyryl-14-acetyl-2E, 8EZ, 10E-atriacylentriol, 12-methylbutyryl-14-acetyl-2E, 8EZ, 10E-atriacylentriol isomer, and linoleic acid isomer were lost after its compatibility with crude Paeoniae Radix Alba. For processed Atractylodis Macrocephalae Rhizoma, compounds 9, 20, 26, 27, and 30 were not found except the relative contents of compounds 5, 6, and 8 were decreased while those of compounds 15, 19, 21, and 31 were increased after its compatibility with processed Paeoniae Radix Alba. Furthermore, compound 4 (protocatechuic acid isomer II) was not found in processed Atractylodis Macrocephalae Rhizoma but could be detected in processed Paeoniae Radix Alba-Atractylodis Macrocephalae Rhizoma herbal pair by using Exact Finder and MassFrontier softwares. The above results illustrated that Paeoniae Radix Alba significantly changed the components of Atractylodis Macrocephalae Rhizoma in solution when they decocted together. The corresponding results were presented in Figure 5 and Table 2.

4. Conclusions

Q Exactive high-performance benchtop quadrupole-Orbitrap LC-MS/MS is a powerful tool for discriminating the chemical changes between single herbal and co-decocting medicines. In our present study, the Q Exactive high-performance benchtop quadrupole-Orbitrap LC-MS/MS based on chemical profiling approach to investigate and evaluate chemical changes from crude and processed Paeoniae Radix Alba, crude and processed Atractylodis Macrocephalae Rhizoma, and their crude and processed herbal pair extracts was proposed. The results showed that processing and compatibility of TCM could significantly change the chemical composition of Paeoniae Radix Alba and Atractylodis Macrocephalae Rhizoma. The developed

method is considered to provide a scientific foundation for deeply elucidating the processing and compatibility mechanism of *Paeoniae Radix Alba* and *Atractylodis Macrocephala Rhizoma*.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Gang Cao, Qinglin Li, Hao Cai, and Sicong Tu contributed equally to this work.

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